University of Alberta

A Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of Quetiapine as Add-on Therapy to the Treatment of Non-Psychotic Unipolar Depression (NPUD) with Residual Symptoms and Sleep Disturbance

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirement for the degree of Master of Science

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Abstract

There are limited data on the effectiveness of the atypical antipsychotic quetiapine as an augmentation agent for non-psychotic unipolar depression (NPUD), despite its frequent use for this purpose. Sixteen patients with residual symptoms of NPUD after at least 6 weeks of antidepressant treatment were randomized into placebo and quetiapine groups for 8 weeks. Analysis demonstrated significantly greater ($p<.05$) mean changes in the 17-item Hamilton Depression Scale (11.875 vs. 4.86, $p=.018$), Montgomery-Asberg Depression Scale (14.88 vs. 5.29, $p=.007$), and Hamilton Anxiety Scale (11 vs. 4.14, $p=.007$) for the quetiapine group ($n=8$) versus the placebo ($n=7$) group. Trends towards improvement were seen in other scales of sleep and disability. Average dosage of quetiapine was 350mg and there were no differences in weight gain, cholesterol, or glucose between groups. This study demonstrates the benefit of quetiapine as an adjunctive NPUD treatment. Limitations include small sample size and no objective measures of sleep.

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List of Abbreviations

AAP	Atypical Antipsychotic
ACTH	Adeno-Corticotrophic Hormone
AD	Antidepressant
AP	Antipsychotic
AST/ALT	Aspartate Aminotransferase/Alanine Aminotransferase
BDNF	Brain Derived Neurotrophic Factor
BMI	Body Mass Index
BPRS	Brief Psychiatric Rating Scale
BUN	Blood Urea Nitrogen
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CNS	Central Nervous System
DBAS	Dysfunctional Attitudes and Behaviors About Sleep
ECT	Electroconvulsive Therapy
EKG	Electrocardiogram
EPS	Extrapyramidal Symptoms
GAD	Generalized Anxiety Disorder
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
HAM-A	Hamilton Anxiety Scale
HAM-D17	Hamilton Depression Scale (17 item)
HDL	High Density Lipid/Lipoprotein
HgbA1c	Hemoglobin A1c (measure of blood sugars
HPA	Hypothalamic-Pituitary-Adrenal
ITT	Intention to Treat
LDL	Low Density Lipid/Lipoprotein
LOCF	Last Observation Carried Forward
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Monoamine Oxidase Inhibitors
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Corpuscular Volume

MDD	Major Depressive Disorder
MINI	MINI International Neuropsychiatric Interview
NE	Noradenaline (norepinephrine)
NMDA	N-methyl-D-asparate
NNT	Number Needed to Treat
NPUD	Non-Psychotic Unipolar Depression
OCD	Obsessive Compulsive Disorder
PD	Panic Disorder
PFC	Pre-Frontal Cortex
PLM	Periodic Limb Movements
PSQI	Pittsburgh Sleep Quality Index
PTSD	Post-Traumatic Stress Disorder
RBC	Red Blood Cell Count
REM	Rapid Eye Movement
SD	Standard Deviation
SDS	Sheehan Disability Scale
SSRI	Selective Serotonin Reuptake Inhibitor
SNRI	Selective Norepinephrine Reuptake Inhibitor
TD	Tardive Dyskinesia
TRD	Treatment-Resistant Depression
TSH	Thyroid Stimulating Hormone
WBC	White Blood Cell Count
WHO	World Health Organization

Introduction

Major Depressive Disorder (MDD) is widely well known to be a prevalent problem in today's society. A recent worldwide study by the World Health Organization (WHO) revealed that 11.7% of those sampled had a current depressive disorder (1) and more than 15% of the population was at lifetime risk for developing this illness (2). MDD is currently the fourth leading cause of disability worldwide and expected to rise to second place by the year 2020 (3, 4).

Although current treatments for MDD are effective and tolerable, recent studies indicate that only 40-50% of patients ever reach full remission from the illness (5). Even up to half of people who are considered responders (usually defined as a 50% or greater decrease in symptoms as measured by standard depression research scales) still have significant residual symptoms (6). These symptoms have been consistently linked to relapse and a poorer prognosis in MDD (7, 8). Overall, only 30% of patients with depression are without symptoms after initial single antidepressant (AD) therapy (9). Thus, there is a great need for improved treatment of MDD.

This need has been long known, and the literature is filled with reports of MDD treatment with combinations of ADs and augmentation with non-antidepressant medications. These are reviewed and summarized extensively elsewhere (10, 11). Notwithstanding good recent systematic trial evidence for some of these

strategies (12-16), most of the data on these are anecdotal and of limited rigor (11). This is in direct contrast to the abundance of good scientific data on single agent AD therapy for the treatment of depression. Therefore, there is a need for further controlled studies on combination and augmentation treatments for depressed patients. Combination and augmentation treatment in MDD is often necessary because of the heterogenous nature of the illness and its effects on the brain.

Antipsychotic (AP) medications have historically been used to create or augment antidepressant response. Imipramine, the original tricyclic AD, is a derivative of chlorpromazine, the original AP. There is a large body of data showing that the first generation or "typical" APs, especially low potency ones such as chlorpromazine, can be comparable to ADs in their effect on depressed patients (17). It is also well known that augmenting an AD with an AP will markedly enhance the acute and long-term response rate of depression with psychotic features (18).

Augmentation with the typical APs has always been limited by the possibility of serious side effects, namely extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) (19). Mood disorder patients (i.e. with bipolar disorder or MDD) are felt to be particularly vulnerable to these side effects compared to schizophrenics (20). The advent of the "atypical" or second-generation antipsychotics (AAPs) such as olanzapine, risperidone, clozapine, quetiapine,

aripiprazole and ziprasidone has reduced the likelihood of these adverse events. These agents have been shown to be as effective as the typical APs while showing lower rates of EPS and TD than the typical APs (21-23), although mood disorders patients are still felt to be more vulnerable to EPS and TD from the AAPs as well (24). Varying degrees of metabolic dysregulation such as weight gain, dyslipidemia and diabetes have limited use to some degree with the first four agents, but not ziprasidone and aripiprazole. Unfortunately, neither of the latter two are easily available in Canada.

Though the findings of superior tolerability and efficacy of the AAPs versus the typical APs have recently been called into question in schizophrenia (25, 26), the strategy of antipsychotic augmentation in depressive syndromes is now being re-examined with the AAP group. Part of the reason for this is that many of these agents appear to be consistently superior to the older medications in the treatment of mood states. This was first noted with the superior benefit of many AAPs in the treatment of depressive symptoms in schizophrenia (27). There are excellent data for olanzapine as monotherapy for the maintenance treatment of bipolar disorder, comparable to lithium, long the gold standard of bipolar disorder treatment (28, 29). Since bipolar patients spend most of their illness in depression (30), some antidepressant effect is likely to be occurring for any successful maintenance treatment of bipolar disorder. Treatment with both olanzapine + fluoxetine (31, 32, 33), as well as recent large scale double blind controlled trials with quetiapine (34, 35), have also demonstrated robust

improvement in the depressed phase associated with bipolar disorder. The evidence is of such strength that they are considered first or second line treatments for bipolar depression in recent published clinical guidelines (36, 37).

Not surprisingly, there is now a burgeoning literature for the AAPs as an adjunctive treatment in non-psychotic unipolar depression (NPUD) (38). This is already seen in common clinical use. A recent chart review demonstrated that 55% of hospitalized NPUD patients were on an antipsychotic (39). Olanzapine (40-42), aripiprazole (43, 44) and ziprasidone (45) all have demonstrated antidepressant effects as augmentation for NPUD in controlled trials. The evidence for olanzapine appears to be more robust and includes double-blind controlled trials (40, 41) and even one open trial of successful monotherapy (46). An olanzapine and fluoxetine combination appeared have a quicker onset of action compared to standard ADs in one study as well (41). The findings with risperidone as a NPUD augmentation agent have been mixed. An early open case series (47) and controlled trials (48, 49) have demonstrated success, but there was an overall failure to improve over placebo in an open 6-month continuation phase of a double-blind trial (50). The use of AAPs in NPUD is reviewed in further detail elsewhere (51, 52).

Quetiapine also appears to possess some antidepressant qualities. Preclinical data demonstrated significant improvement in animal paradigms of conditioned avoidance (53) and drug-induced social isolation, similar to other AAP agents

(54). Although these tests are considered behavioral models of antipsychotic activity, both could also be considered models for the depressive symptoms of isolation and anxiety. Improvements in conditioned avoidance and drug-induced social isolation have been seen with AD medication as well (55). Interestingly, in both paradigms quetiapine demonstrated significant improvement in higher animals (cats and monkeys) but none in lower mammals (rats) (53, 54), indicating a potential selective benefit in humans.

The first indication of the antidepressant effect of quetiapine in humans was seen in secondary meta-analyses from the early double-blind trials of the drug in schizophrenic patients. These demonstrated the superiority of the agent over haloperidol and placebo on both depressive and anxiety symptom clusters as measured by the brief psychiatric rating scale (BPRS) (56). Data from a large, open, randomized trial in a heterogeneous psychotic patient population have shown robust antidepressant response superior to risperidone on the Hamilton Depression Scale (HAM-D) (57, 58). These findings further evolved into open-trial evidence of the efficacy of quetiapine for mood symptoms in psychotic mood disorders (59, 60). Not surprisingly, anecdotal success of quetiapine augmentation for depressive symptoms in many other areas has followed (61). Open trial data showing potential antidepressant efficacy have been seen in augmentation trials for post-traumatic stress disorder (PTSD) (62, 63) and borderline personality disorder (64, 65). Placebo-controlled double-blind trial data have been seen for quetiapine augmentation in resistant obsessive compulsive

disorder (OCD) (66), and most recently as monotherapy in two landmark large scale multi-centre trials in bipolar depression (34, 35). Secondary subanalyses of these two studies demonstrated a favorable effect size, and a possible anti-suicidal effect (67). Recent evidence is now demonstrating potential antidepressant and anxiolytic effects for quetiapine monotherapy in alcohol dependence (68), social anxiety (69, 70), and generalized anxiety disorder (GAD) as well (71).

In terms of adjunctive quetiapine in the treatment of NPUD, there are 3 case series (72-74), one comparative open label trial demonstrating the superiority of quetiapine to lithium augmentation in patients with residual symptoms (75), and one open follow-up trial of 20 weeks (76). There are also two studies of quetiapine plus AD versus placebo plus AD combination therapy in medication-free patients at the beginning of MDD treatment. One was a single-blind placebo controlled trial comparing a paroxetine group and a paroxetine plus quetiapine group over 8 weeks (77). The other was an open label 4-week study demonstrating an improvement in sleep and mood after adding a rapidly titrated antidepressant and quetiapine to resistant patients after a 3-day washout of previous medications (78).

Finally, a recent study also demonstrated that quetiapine had similar efficacy to amitriptyline in an animal model of anhedonia (82). Similar to the current trial, there also have been two recent double-blind placebo-controlled trials of

quetiapine augmentation of AD in patients with residual symptoms of depression. These studies were of very similar design to the thesis and many comparisons will be made throughout this paper. Both demonstrated a robust effect of adjunctive quetiapine treatment versus placebo in NPUD (79, 80). Another double-blind study also demonstrated significant improvement for the quetiapine group but focused on augmentation in NPUD with prominent residual somatic symptoms (81). Hence there is a significant evidence base demonstrating the potential antidepressant efficacy of quetiapine in NPUD augmentation treatment.

Quetiapine is also very well tolerated, with levels of EPS comparable to placebo (83) and high patient acceptability in long-term treatment (84). Major side effects are minimal and include sedation, a small amount of weight gain, as well as orthostatic hypotension (83, 84). In addition to its potential antidepressant effect, quetiapine has a very favorable side effect profile and limited drug interactions (85). There are no major interactions with members of two major AD classes, the selective serotonin uptake inhibitor (SSRI) fluoxetine and the tricyclic imipramine (86). Quetiapine is primarily metabolized by the cytochrome P450 3A4 enzyme (CYP3A4) (87), and thus it may interact with drugs that utilize this enzyme. However, this effect appears to be minimal (88). These two features above make quetiapine an attractive option as an adjunctive treatment for depression in community settings.

As mentioned previously, long-term metabolic and weight concerns have been a large problem with the AAP group. Postulated mechanisms include H1 antihistamine receptor blockade and 5HT2C receptor activity and the reader is referred elsewhere for a full review of this topic (89-92). These issues are of crucial importance, not only because of numerous related health issues, but also due to medication compliance rates. Obese people have been shown to have over twice the amount of non-compliance with the AAP group compared to non-obese patients (93).

The weight gain for quetiapine has been estimated at between 2-4kg over 1 year in long-term studies (94). Similar to many other AAPs, weight gain, hyperlipidemia and glucose dysregulation are all significant possibilities with quetiapine. Data are mixed, but overall it appears that quetiapine has demonstrated fewer of these metabolic difficulties than AAPs such as clozapine and olanzapine and is similar to risperidone at a moderate level of metabolic risk (89,92). Clinically, the metabolic difficulties of quetiapine and other AAPs appear to be clinically related to dosages to some degree, although this has not always been borne out by controlled studies (95). Given that the AAP augmentation in NPUD appears to generally require lower dosages than schizophrenia treatment, this makes the potential metabolic risk of quetiapine in this area even lower. Aripiprazole and ziprasidone are both AAPs that are likely metabolically and weight-neutral (92) and may hold great promise as NPUD augmentation agents,

but as mentioned previously, neither of these is readily available in Canada (at the time of this writing).

Disturbed sleep and anxiety are two symptom domains in depressed patients that are worth independent examination in their own right. Both are well known to be commonly co-morbid in depression and are strongly linked to treatment difficulties, poor outcomes and overall non-response (96-98). It has long been clinical practice to use AP medication to reduce agitation, anxiety and sleep fragmentation in non-psychotic depression (99). These symptom domains appear to be areas of significant advantage for the AAP and good evidence is emerging for their role in several anxiety disorders (99). Quetiapine also appears to significantly reduce various domains of anxiety symptoms in the large bipolar depression trials (100), anxiety disorders (62, 63, 65, 69-71) as well as other augmentation trials in NPUD (79).

Although often measured as an item on scales of mental illness, the specific effects on sleep in psychopharmacological studies have rarely been looked at independently. The reason for this is likely multifactorial, and potential contributors include poor training about sleep disorders in psychiatry, a lack of psychiatrists trained in sleep medicine, and the unavailability of sleep laboratory facilities for research in many jurisdictions. Hence it is not surprising that there is very little evidence of the effects of the AAP group on the subjective and objective variables of sleep. Subjective sleep in patients with schizophrenia and

bipolar disorder have been seen to improve after a switch to AAP treatment from typical AP treatment (101, 102). Other AAPs (olanzapine, clozapine, risperidone and ziprasidone) have shown to objectively increase stage 2 slow wave sleep, as well as sleep continuity in healthy volunteers (103-105) and schizophrenics (106, 107). Interestingly, an improvement in objective sleep parameters similar to sedating antidepressants has also been seen with both olanzapine and risperidone when added to patients with treatment resistant depression (108, 109). Rapid eye movement (REM) suppression and increased REM latency, common objective sleep changes of AD treatment (110, 110a), were also seen in the risperidone study (109) and in healthy people that were given ziprasidone (105).

Clinically, recent open studies of quetiapine in PTSD (111) and Parkinson's (112) demonstrated specific improvements in various domains of subjective sleep. It was also found to significantly improve sleep-wake disturbances compared to haloperidol in patients with Alzheimer's dementia (113). Subanalyses of the sleep items on depression and anxiety rating scales have shown a vast improvement with adjunctive quetiapine use in NPUD (76, 79). This has been seen with other AAPs (41, 42), although clinically quetiapine is thought to be one of the more sleep-promoting AAPs.

There are only two known studies measuring the effects of quetiapine on variables of objective sleep measured by polysomnography. The amount of total

sleep time, sleep efficiency and sleep latency improved in one study of healthy subjects and there was a significant increase in periodic limb movements (PLM) (114), a polysomnographic finding of recurrent leg twitching that is of unclear clinical significance. There was significant REM suppression and a trend toward increased REM latency, which as mentioned earlier, are objective sleep effects of almost all antidepressants of different classes (110). The other study (115) used quetiapine in patients with primary insomnia, which is sleep disturbance without any overt psychiatric or medical pathology. Patients in the quetiapine group also demonstrated a significant increase in total sleep time, sleep efficiency and a decrease in subjective sleep latency but no decrease in objective sleep latency. There were no significant effects on REM sleep reported. Another previously mentioned study (78) indicated that adjunctive quetiapine treatment was beneficial for sleep in NPUD because of a reduction in nighttime variables of motor restlessness measured by actigraphy, which can approximate true sleep. However, as discussed later in this thesis, this study has significant methodological problems on both the sleep and mood fronts.

Given this rapidly evolving evidence base of an antidepressant effect with adjunctive quetiapine and other AAP treatment, as well as the tolerability of quetiapine compared to other AAPs, it was felt that a pilot placebo-controlled study of quetiapine in non-psychotic depression was warranted. The effects of quetiapine on anxiety symptoms, sleep, weight, cholesterol and glucose levels were also warranted as secondary objectives.

Objectives & Hypotheses

This study attempted to answer the question of whether or not quetiapine is a viable augmentation strategy for patients with residual symptoms of NPUD after 6 weeks of SSRI or serotonin noradrenaline reuptake inhibitor (SNRI) therapy. The safety and overall clinical tolerability of quetiapine in this patient population were also assessed. The population was limited to persons who were already on SSRI/SNRI agents, in order to create a more homogenous study group and because of the wide use of these drugs in depressive disorders.

Based on the aforementioned rationale and previously reported data, the hypothesis of the study was that the use of quetiapine, compared to the placebo group, would demonstrate:

1. Significant antidepressant and anxiolytic effects when both were added to the treatment regimen of patients who have residual symptoms of non-psychotic depression on SSRI/SNRI therapy.
2. A small amount of weight gain, but no adverse change in cholesterol or glucose levels.
3. A beneficial effect on sleep.

Methods

Patients were recruited through the outpatient psychiatry clinics at the Grey Nuns Hospital in Edmonton, and through the practices of local psychiatrists and general practitioners. Radio advertisements to the public were also used to attract potential subjects. The study protocol and all advertisements were approved by the University of Alberta Research Ethics Board.

Pre-study screening: All patients were telephone-screened by the author and a research assistant. After basic inclusion and exclusion criterion were applied, potential patients were asked to present for an interview. Informed consent was obtained and detailed inclusion and exclusion criteria (see below) were reviewed through patient interviews.

A. Inclusion Criteria

1. Ages 18-65.
2. Current episode of MDD without psychotic features as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (116) criteria. This was determined according to clinical interview and the MINI International Neuropsychiatric Interview (MINI) (117). The MINI is a brief structured interview designed to systematically screen for the major axis I disorders in the DSM-IV-TR. Studies demonstrate its comparable reliability and validity to other structured research interviews, and has gained wide clinical acceptance.

3. At least 6 weeks of single agent SSRI or SNRI therapy at an acceptable dose (5, 118) (see Table MT-1) in the current episode.
4. Residual symptoms of depression still present after this treatment. The 17-item Hamilton Depression Scale (HAM-D17) (119) was used to determine this. The HAM-D17 is a clinician-rated scale that is assessed after a semi-structured interview. It has been the gold standard and the main outcome variable for over 40 years in depression research trials (6). A HAM-D17 score equal to or above 16 after 6 weeks of a therapeutic dose of AD treatment is considered an indication of residual symptoms. According to the HAM-D17, 16 or greater is the minimum cutoff point for moderate depression, and this definition has been used in well-accepted controlled augmentation trials of antidepressants in NPUD (120-122). A HAM-D17 score of 16 or above after treatment with a therapeutic dose of AD after 6 weeks is also one of the many definitions of treatment-resistant depression (TRD) and has been sub-classified as a definition of Level 1 or early treatment resistance (123, 124).
5. Female patients on an accepted method of contraception.

B. Exclusion Criteria

1. Substance abuse as defined by the MINI.
2. Serious unstable illness or other illness felt upon clinical interview to interfere with study (e.g. newly controlled diabetes).
3. Clinically significant disturbance on laboratory indices (see List MT-2) as determined by study physicians.
4. Use of herbal products for depression/anxiety.

5. History of electroconvulsive therapy (ECT) in previous 6 months.
6. Any history of treatment with clozapine.
7. Any concomitant serious psychiatric disorder except for secondary Panic Disorder (PD), General Anxiety Disorder (GAD), PTSD, social phobia or OCD, diagnosed by clinical assessment or MINI interview.
8. Any history of a psychotic, hypomanic or manic episode according to the MINI.
9. Severe cluster A traits, borderline, or antisocial personality disorder according to DSM-IV-TR criteria or determined by clinical interview.
10. Known allergy to quetiapine.
11. Serious suicidal risk as assessed by clinical interviewer.
12. Pregnancy, lactation or intention to become pregnant.
13. Any antipsychotic medication in previous 4 weeks.
14. Any other prescription central nervous system (CNS) medication except for benzodiazapines, zopiclone, zalepon and trazodone. These were washed out over 2 weeks prior to the study medication beginning.
15. Other concomitant medication felt to interfere with study or cause a safety risk according to clinical judgment (see Table MT-3 for detail).
16. Patients on nefazodone or other strong cytochrome P450 3A4 blockers, as these have been shown to elevate the level of quetiapine (87).
17. People who had started formal psychotherapy or light therapy in the previous 8 weeks.
18. Patients with unexplained problems of vision or previous exposure to radiotherapy of the head, as well as past prolonged systemic exposure to

corticosteroids. This was done to reduce the risk of cataract formation, which was a small risk of quetiapine treatment at the time of the study based on animal studies. It is now not an issue in the human use of quetiapine (125).

C. Premature withdrawal or discontinuation criteria

1. Clinical deterioration as determined by the study doctors.
2. A serious adverse event.
3. Patient's voluntary choice to stop participation in the study at any time. This did/would not affect their future medical care.
4. Noncompliance with study procedures.

Baseline evaluation: Patients satisfying baseline criteria underwent a physical examination performed by the author. Blood tests were then performed with various standard hematological, chemistry and urinalysis panels (see List MT-2 for detail). In large-scale clinical trials, quetiapine has shown no major complications of these panels except for transient liver enzyme elevation, small dose-related increases in total and free levothyroxine (with no thyroid stimulating hormone [TSH] elevation) and a potential increase in cholesterol, glucose and hemoglobin A1c, a long term marker of glucose levels concentrations (126).

Method of randomization, blinding, comparative agent: If a subject satisfied all criteria and consented, he or she was randomized in double-blind fashion by a computer program to either receive placebo or quetiapine in addition to their current medication. The ratio of randomization was 1:1. Prior AD therapy in both

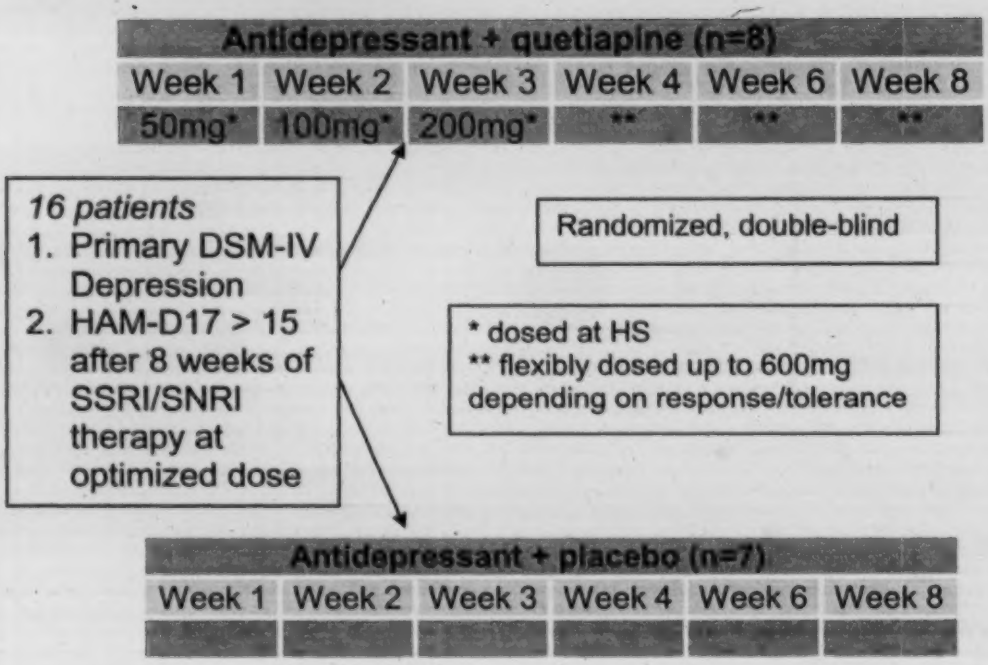
groups was continued. This has been discussed in the literature as an ethical design because it is often noted that more than 6 weeks is needed to respond to single agent AD therapy (123, 127).

Concomitant medication: Concomitant medication was monitored throughout the study and certain medications were allowed (see Table MT-3). The only CNS active medication allowed throughout the study was lorazepam as necessary at a maximum rate of 4mg per week.

Drug formulation, dosage regimen: Initially, patients in the active group were titrated flexibly towards a target dose of 200mg over 3 weeks. The schedule for dosing was 50mg at night for 7 days, 100mg at night for 7 days, and then 200mg at night for 7 days. After this, the dose was titrated as necessary to a maximum of 600mg at night. All dosing was done at the discretion of the investigators, using patient tolerance and response as guidelines. The dosage was not increased at a rate more than 200mg per week and was done in 100mg increments where possible. The dose of 200mg is within range of the average dose of quetiapine use in large naturalistic studies of non-psychotic disorders (52, 61), and the two other double-blind NPUD augmentation trials had a similar dosing schedule (79, 80). This titration is actually much slower than the recommended titration schedule on the package label (126).

Treatment visits: Patients were seen at 1, 2, 3, 4, 6, and 8 weeks (+/- 2 days on each visit). Efficacy scales, disability measures and adverse event categorization were performed at each visit (Figure MF-1, Table MT-4). At the last visit, repeat blood work indices of fasting glucose and lipid levels were performed. After the study's completion, the patients were given the option to continue follow-up at either the Grey Nuns outpatient clinic or return to the point of referral if applicable.

Figure MF-1: Study Design



Efficacy, variables and analysis:

The basic hypothesis was subdivided into primary and secondary objectives as follows:

Primary Objective

This was the last observation carried forward (LOCF) mean change from baseline to endpoint on the HAM-D17 for both groups for the intention to treat (ITT) population. The ITT was defined to be any patient who started the study, took study medication and had one set of assessments after baseline. For the purposes of this study, response was defined as a fifty percent decrease in the score over 8 weeks. Remission was defined as a total HAM-D17 score of less than 8. These are consistent with the standard definitions in the literature (5, 10).

Secondary objectives

The secondary objectives of this study were to compare the efficacy, safety and quality of life changes of 8 weeks of quetiapine augmentation therapy versus placebo using the following assessments: [1]

1. Montgomery-Asberg Depression Rating Scale (MADRS) (128). The MADRS is a scale that is now in widespread use. It consists of 10 items ranked by the clinician on a scale of 0 (no symptoms) to 6 (most severe) after a semi-

[1] All are LOCF mean change from baseline to endpoint for both groups (in the ITT) unless mentioned otherwise.

structured interview. It is thought to be more sensitive to change in AD trials than the HAM-D (129,130).

2. Treatment of anxiety symptoms. This was measured by the Hamilton Anxiety Scale (HAM-A) score (131). The HAM-A is the most widely used observational rating scale for anxiety. It has 14 items scored by the clinician from 0 (no symptoms) to 4 (very severe) after a semi-structured clinical interview. A HAM-A of 15 or above is considered a moderate level of baseline anxiety.
3. Change on the Clinical Global Impressions – Severity and Improvement (CGI-S & CGI-I) (132). The CGI-S and CGI-I are simple 7-point clinician-rated scales that categorize the degree of improvement and severity. The CGI-I is rated from very much improved (1) to very much worse (7), while the CGI-S is rated from normal or not ill (1) to among the most extremely ill of all patients (7). These scales have the advantages of being simple to use and clinically relevant.
4. Weight gain, fasting lipid and glucose changes by measuring the mean change in standard indices of cholesterol levels and glucose over the 8 weeks of treatment, as well as measuring weight throughout.
5. Change from baseline to endpoint on the Pittsburgh Sleep Quality Index (PSQI). The PSQI (133) is a well-validated scale used to globally measure patients' subjective feelings about their quality of sleep. It is filled out by the patient and consists of nine general questions, which are then scored by the clinician into seven factors of sleep quality. Other sleep measurements

included the total sleep subscale on the HAM-D17, (which consists of 3 items: initial, middle and later insomnia) and the global sleep subscale of both the HAM-A and the MADRS.

6. Quality of life of patients: this was measured by the Sheehan Disability Scale (SDS) (134). This is a simple patient-rated 3-item scale, which is a well-validated instrument for the assessment for perceived disability from illness. The items are rated from 0 to 10 (10 being severe disruption).
7. Standard research definitions of response (a 50% or greater decrease in HAM-A and MADRS scores) and remission rates (HAM-A below 8, PSQI below 5, or MADRS below 11) (6, 10). Response on the CGI-I and CGI-S was defined as people with greater than 1 point of improvement on either scale. Remission was considered a score of 1 or 2 on either scale. Again, this is consistent with the predominant definitions in the mood disorders literature (6, 118, 123).
8. Change from baseline on various individual PSQI, MADRS, HAM-D, HAM-A item scores. The entire protocol is summarized in Table MT-4.

Sample size:

In terms of power, the study was originally designed to have 20-25 subjects in each arm. Approximately 60 total patients would have to be randomized to achieve this goal. From basic statistical tables, a study of this size is sufficient to show an effect size that is 80-90% of the standard deviation (SD) of change between the means of the placebo and active groups. This is when using the t-

test (test for comparing means of continuous variables) and the assumptions of 2-tailed alpha value of =0.05 and a beta value of =0.20.

The SD of the expected change on the Hamilton depression scale (HAM-D17) between placebo and active medication groups is approximately 6 points. This figure is a composite estimate from data including: past controlled studies of AAP augmentation of non-psychotic unipolar depression (40, 79) and typical AP augmentation data (17).

Thus this sample size would have been able to detect a difference of at least (0.8*6 =) 4.8 to (0.9*6 =) 5.4 points between the placebo and active treatment groups using the measure of mean HAM-D17 scores. This difference is well within the expected effect size, given past reports on other anti-psychotic augmentation trials in other forms of depression (17, 34, 35, 40). A similar sample size to the current study has also been used in previous controlled trials of augmentation with other agents (40, 120-122) and this trial is a pilot study as well.

Basic Statistical Analysis

All analyses were done on the intention to treat (ITT) population. Demographic variables were compared between the placebo and active treatment groups. T-

tests were used to determine this significance between groups on continuous variables, and Chi-square tests were used on dichotomous variables.

The analysis consisted of the mean differences on all outcome measures from baseline to week 8 (LOCF) between treatment groups. Comparison between placebo and quetiapine groups was done using t-tests. All tests were 2-tailed with a significance level set at $p<.05$ unless otherwise stated. Trends towards significance were defined as $p=.05$-0.1. Mean changes at each visit were calculated for major outcome measures and compared with t-tests as well.

Response, remission rates, average dosage and safety data were compared with various descriptive statistics. The SPSS statistics software package was used to assist in the primary and secondary analysis of data.

Unfortunately, expected enrollment was not feasible, and the study group consisted of 8 patients for each arm. This compromised the power of this study. Analysis of objectives still went ahead as previously outlined, but descriptive statistics often had to suffice given the limited subject population. However, the current study was only designed to be a pilot and not meant to be definitive.

Table MT-1: Acceptable Antidepressants and Adequate Dosage[b]

Antidepressants[a]		Adequate Dose (mg/day)
SSRI	Citalopram	40
SSRI	Fluvoxamine	150
SSRI	Paroxetine	40
SSRI	Sertraline	150
SNRI	Venlafaxine	150
SSRI	Fluoxetine	40

[a] Acceptable antidepressant trials - 6 weeks as the minimum adequate dose listed above from history or chart

[b] Drug and dose criteria (5, 84a)

List MT-2: Laboratory Tests

Hematology

Hemoglobin, hematocrit, RBC, MCV, MCHC, WBC, lymphocytes, monocytes, neutrophils, eosionphils, basophils, platelets, cell morphology, Hemoglobin A1C

Urine

Standard urinalysis, urine drug screen for solvents, opioids, marijuana, cocaine, amphetamines, urine B-HCG (females only)

Chemistry

Sodium, potassium, chloride, calcium, phosporous, creatine, BUN, uric acid, bilirubin, alkaline phosphatase, GGT, AST/ALT, total protein, albumin
TSH*, fasting glucose, cholesterol, triglcyerides, LDL, HDL
EKG (interpreted by cardiologist on staff at hospital)

* If TSH is abnormal a free T4 index will be done to determine clinical significance

Table MT-3: Drugs Allowed (Y) and Not Allowed (N) as Concomitant Medications (drugs not included were assessed at the discretion of the study doctor)

Drug Class	Episodic Use	Chronic Use
H_2 Blockers	Y	Y
Antihistamines	Y	Y
Steroids (topical, ophthalmic or inhaled)	Y	Y
Other steroids	N	N
Antiemetics	Y	N
Antihypertensives	N	Y
Ace inhibitors	N	Y
Beta blockers	N	Y
Calcium channel blockers	N	Y
Thyroid hormone supplements[a]	N	Y
Benzodiazepines[b,c]	N	N
Accutane	N	N
Amantadine	N	N
Anorexics (i.e. appetite suppressants, diet aids, weight loss aids)	N	N
Antiarrythmics	N	N
Anticoagulants	N	N
Anticholinergics	N	N
Anticonvulsants	N	N
Antipsychotics[d]	N	N
CNS herbals	N	N
Erythromycins	N	N
Hormones (not including estrogen replacement therapy and insulin)	N	N
Anti - Parkinsonians	N	N
Narcotics	N	N
Psychositimulants	N	N
Tryptophan	N	Y
Hypnotics (sleep aids)[c]	N	Y

(inhaled steroids added because of low interaction potential and common usage)

[a] Stable dose for more than 6 weeks

[b] Lorazepam (up to 4mg/week) is allowed

[c] Will be washed out over 2 weeks

[d] None in previous 4 weeks

Table MT-4: Study Flowsheet

	Screen	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8
Study Day (+/-1 day)	-14	0	7	14	21	28	42	54
Visit No	1	2	3	4	5	6	7	8
Consent	x							
Medical/ Psychiatric HX	x							
MINI	x							
Prior meds	x							
Concomitant meds[1]	x	x	x	x	x	x	x	x
Drug or placebo[2]		x	x	x	x	x	x	x
Efficacy								
HAM-D 17	x	x	x	x	x	x	x	x
MADRS		x	x	x	x	x	x	x
HAM-A		x	x	x	x	x	x	x
CGI-I		x	x	x	x	x	x	x
SDS		x	x	x	x	x	x	x
PQSI		x	x	x	x	x	x	x
Safety								
Phys exam	x							
Vitals[3]	x	x	x	x	x	x	x	x
Weight	x	x	x	x	x	x	x	x
Lab tests[4]	x							x
ECG	x							
Urine tox	x							
Adverse events			x	x	x	x	x	x
Notes								

[1] see Table MT-3 for list of allowed medications and washout criteria
[2] see dosing pattern discussed in protocol
[3] vitals include pulse, sitting and supine blood pressure, respiration rate, temperature
[4] see List MT-2 for list of blood tests

Results

A large number of people (350) were telephone screened and 24 of these people were deemed suitable to present for clinical interview. Of these, 2 were excluded due to continued substance abuse and another 6 were found to have bipolar II disorder. Sixteen people were then randomized to the placebo and treatment groups. One person was dropped prior to treatment because of a protocol violation. The patient in question had stopped her AD between randomization and treatment.

Two people dropped out of the study, one person in each group. The person in the placebo group dropped out at week 3, due to non-response. The person in the treatment group dropped out in week 7, also due to non-response. One patient was hospitalized for psychosocial stressors that were clearly non-quetiapine related one day prior to her last set of measurements.

Demographic variables were comparable between the 2 groups (Table RT-1). There were no significant differences. The groups were patients who had between 2-3 trials of ADs and had been depressed for 3-5 years. The groups would be considered obese, with a body mass index (BMI) of 30 and above.

Table RT-1: Demographic and Baseline Depressive Episode Data (standard deviation in brackets)

	Placebo	Quetiapine
Number in group	7	8
Dropouts	1	1
Age	41.43 (11.28)	41.38 (13.14)
Mean weight (kg)	90.13 (21.11)	88.38 (18.50)
Mean height (cm)	169.43 (9.81)	171.25 (7.17)
Mean BMI	31.05 (5.03)	29.97 (4.97)
Gender	3F / 4M	4F / 4M
Mean # of antidepressant trials	2.29 (1.38)	2.50 (1.51)
Mean treated depression time (yrs)	5.78 (3.61)	3.50 (1.31)
Mean current episode length (yrs)	3.93 (3.34)	3.19 (1.67)

Table RT-2 indicates the baseline measurements for the 2 groups on major outcome measures. The treatment group was found to have a statistically more significant level of depression on the primary outcome variable, the HAM-D17. Otherwise there were no significant differences between the groups. Overall, the scores on the HAM-D17, HAM-A and MADRS in both groups fell into the category of moderately depressed and anxious. Patients had a moderate level of disability and severity of illness given the baseline scores on the SDS and CGI-S. However, the groups had severe sleep disturbance as measured by the PSQI. The PSQI for a normal control population is 2.67 and a score of above of 5 has been considered elsewhere to be significant insomnia (101).

Table RT-2: Mean Outcome Variables at Baseline (standard deviation in brackets)

	Placebo	Quetiapine	P value
HAM-D17	***19 (1.53)***	***21.625 (2.50)***	***0.029***
MADRS	27.14 (4.06)	29.25 (4.10)	0.337
HAM-A	19.29 (1.98)	21.38 (4.69)	0.278
SDS	20.21 (6.38)	23.50 (6.30)	0.335
PSQI	10.71 (4.19)	11.13 (2.36)	0.824
CGI-S	4.14 (0.38)	4.50 (0.53)	0.156

In terms of metabolic concerns, there were no significant baseline differences between the groups (Table RT-3), except the placebo group had an average total cholesterol level that was slightly elevated. Otherwise baseline metabolic concerns were well within normal limits.

Table RT-3: Mean Baseline Metabolic Indices (standard deviation in brackets)

Metabolic Indices	Placebo (n=7)	Quetiapine (n=8)	p value
Total cholesterol	5.31 (0.85)	4.90 (0.82)	0.352
LDL	3.37 (0.62)	2.89 (0.88)	0.238
HDL	1.13 (0.19)	1.10 (0.23)	0.748
Triglyceride	1.79 (0.98)	2.00 (1.21)	0.708
Random glucose	4.96 (0.69)	4.93 (0.78)	0.934
HbA_{1C} (%)	5.2 (0.54)	5.4 (0.38)	0.343

Table RT-4 summarizes the LOCF ITT analysis of the mean change in major outcome variables in the study. The quetiapine group demonstrated statistically greater mean change than the placebo group on the primary outcome measure (HAM-D17) and the secondary outcome measures of the HAM-A and the MADRS. This effect started at week 4 (Figures RF-1 to RF-3). Trends towards significance were seen in sleep disturbance (PSQI), overall disability (SDS), as well as the Clinical Global Impression Scales of severity and improvement (CGI-S and CGI-I). The average dose was 350mg (SD 177.21, range 100-600mg) in the treatment group. Only 1 person used benzodiazepines as rescue medication in the study.

Table RT-4: Mean Improvement Over 8 weeks (LOCF ITT analysis, standard deviation in brackets)

	Placebo (n=7)	Quetiapine (n=8)	p value
HAM-D	*4.86 (3.93)*	*11.88 (5.77)*	*0.016*
MADRS	*5.29 (4.79)*	*14.88 (6.62)*	*0.007*
HAM-A	*4.14 (4.01)*	*11.00 (4.21)*	*0.007*
PSQI	*3.29 (2.56)*	*6.00 (3.81)*	*0.128*
CGI-S	*0.57 (0.53)*	*1.38 (0.92)*	*0.058*
CGI-I	1.0 (0.82)	1.875 (1.36)	0.162
SDS	*1.93 (4.49)*	*7.19 (6.93)*	*0.112*

Figure RF-1: Mean Improvement in HAM-D17 Over 8 weeks (*p<0.05 vs. placebo, LOCF ITT analysis, 2-tailed t-test)

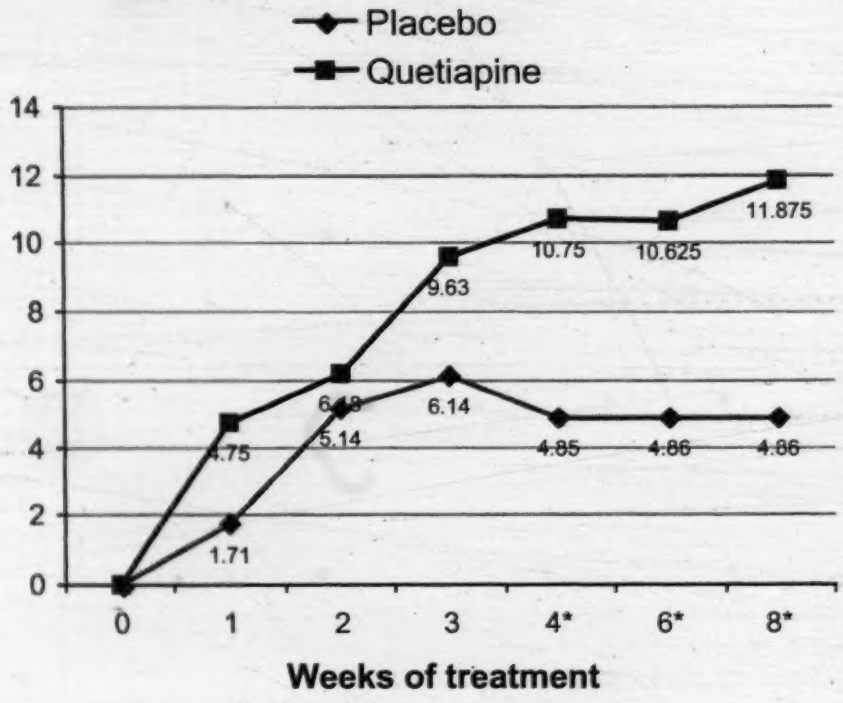


Figure RF-2: Mean Improvement in MADRS Over 8 weeks (*p<0.05 vs. placebo, LOCF ITT analysis, 2-tailed t-test)

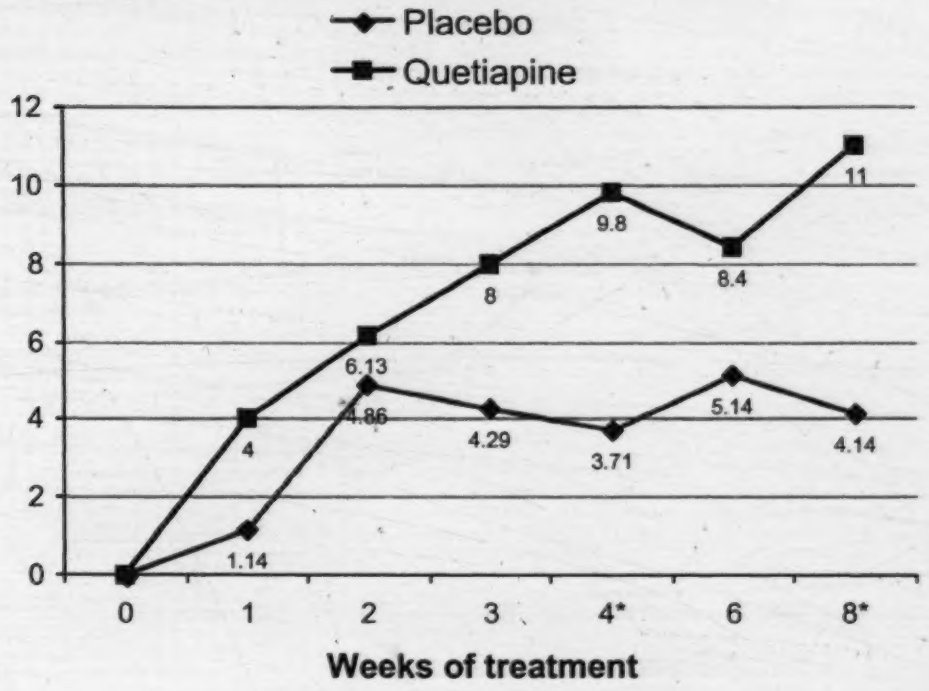
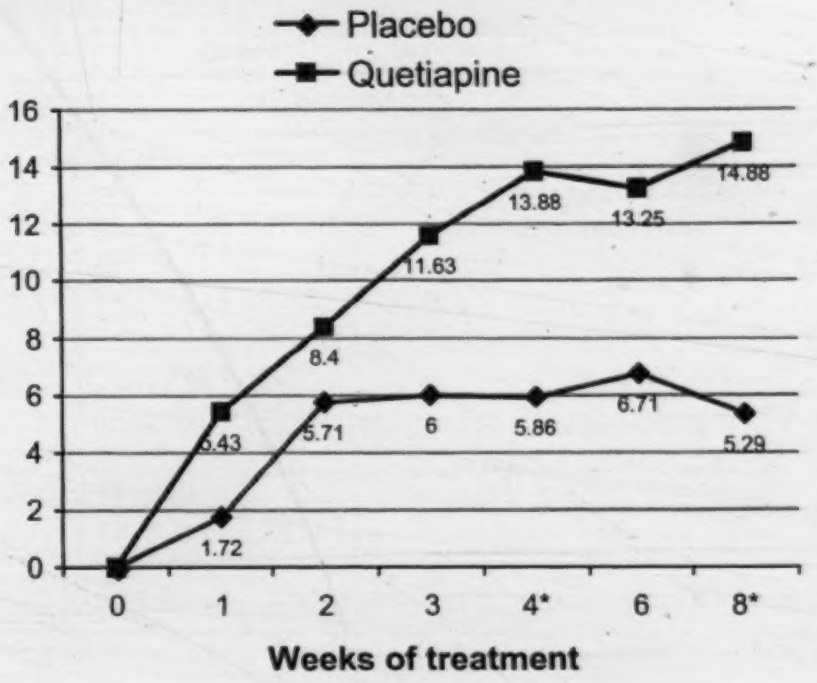


Figure RF-3: Mean Improvement in HAM-A Over 8 weeks (*p<0.05 vs. placebo, LOCF ITT analysis, 2-tailed t-test)



Looking at the various response and remission rates (Table RT-5), there are numerically more responders and remitters in the quetiapine group on many of the outcome measures. A significant difference was seen in HAM-A response rates and trends towards significance are seen for remission rates on the HAM-D17, MADRS and CGI-S, and for response rates on the PSQI, MADRS, CGI-S and CGI-I. No statistically significant metabolic changes were seen (Table RT-6).

Table RT-5: Response and Remission Rates

	Placebo (n=7)	Quetiapine (n=8)	p value
HAM-D Response[1]	2/7 (32%)	4/8 (50%)	0.398
HAM-D Remission[2]	*0/7 (0%)*	*3/8 (37.5%)*	*0.070*
HAM-A Response[1]	1/7 (14%)	4/8 (50%)	0.143
HAM-A Remission[2]	**0/7 (0%)**	**4/8 (50%)**	**0.029**
PSQI Response[1]	*1/7 (14%)*	*5/8 (62.5%)*	*0.070*
PSQI Remission[3]	2/7 (32%)	4/8 (50%)	0.398
MADRS Response[1]	*0/7 (0%)*	*3/8 (37.5)*	*0.070*
MADRS Remission[4]	*0/7 (0%)*	*3/8 (37.5%)*	*0.070*
CGI-I Response[5]	*2/7 (32%)*	*6/8 (75%)*	*0.072*
CGI-I Remission[6]	1/7 (14%)	4/8 (50%)	0.143
CGI-S Response[5]	*0/7 (0%)*	*3/8 (37.5%)*	*0.070*
CGI-S Remission[6]	*0/7 (0%)*	*3/8 (37.5%)*	*0.070*

[1] 50% decrease
[2] score ≤ 7
[3] score ≤ 5
[4] score ≤ 11
[5] 2-point change
[6] score either 1 or 2

All tests used Pearson chi-squared test for p-values

Table RT-6: Mean Change in Metabolic Indices After 8 weeks (standard deviation in brackets)

Metabolic Indices	Placebo (n=7)	Quetiapine (n=8)	p value
Weight	0.95 (2.19)	1.23 (2.82)	0.832
Total cholesterol	0.07 (0.77)	0.39 (0.87)	0.471
LDL	0.14 (0.41)	0.28 (0.36)	0.515
HDL	0.046 (0.09)	0.067 (0.15)	0.751
Triglyceride	0.26 (0.84)	0.10 (1.53)	0.582
Random glucose	0.13 (0.59)	0.28 (0.65)	0.628
HbA_{1C} (%)	0.27 (0.0055)	0.01 (0.0035)	0.311

When looking at the sleep variables (Table RT-7), there was only a trend towards significance for the quetiapine group on the PSQI total at week 8. This was powered by statistically significant improvements in item 3 (hours of sleep), item 7, (enthusiasm and mood), as well as a positive trend in item 4 (sleep efficiency). There were also significant differences seen in the quetiapine group for change in PSQI total at week 6 (Figure RF-4). There were trends towards significance starting at weeks 1 and 2 for PSQI items as well, but no consistent significant separation until week 6 (Figures RF-5 and RF-6). There was a significant change in the HAM-D17 total sleep score as well, which was almost entirely due to changes in item 5 (middle insomnia) (Table RT-7). Again, trends towards significance were seen at week 1, but consistent separation was not seen until week 6 (Figure RF-7). The changes in HAM-A and MADRS sleep scores were significant, but these are only one item and hence a more global measure of sleep. Even when the sleep variables were dropped from the total scores, there was still a statistically significant benefit in the quetiapine group versus placebo on the HAM-D17, HAM-A, and MADRS.

Table RT-7: Mean Improvement of Sleep Variables Over 8 weeks (standard deviation in brackets)

	Placebo (n=7)	Quetiapine (n=8)	p value
HAM-D17 total sleep score	***1.43 (0.79)***	***3.25 (1.75)***	***0.025***
Early insomnia	0.71 (0.95)	1.13 (0.83)	0.389
Middle insomnia	***0.14 (1.06)***	***1.38 (0.92)***	***0.032***
Later insomnia	0.57 (0.53)	0.75) (0.89)	0.651
MADRS sleep score	***0.71 (0.95)***	***2.89 (1.752)***	***0.014***
HAM-A sleep score	***0.57 (0.53)***	***1.75 (0.89)***	***0.009***
Overall sleep quality	0.71 (0.76)	0.88 (0.99)	0.733
Sleep latency	0.86 (0.89)	0.62 (1.06)	0.658
Hours of sleep	***0.14 (0.69)***	***1.125 (0.99)***	***0.047***
Sleep efficiency	*0.29 (0.49)*	*0.88 (0.64)*	*0.065*
Sleep interruption	0.71 (0.49)	1 (0.53)	0.302
Use of sleep medicine	1 (1.29)	0.625 (1.19)	0.568
Enthusiasm/mood	***-0.42 (1.40)***	***0.88 (0.83)***	***0.044***
HAM-D without sleep	***3.43 (3.69)***	***8.63 (4.75)***	***0.036***
MADRS without sleep	***4.57 (4.35)***	***12 (6.05)***	***0.018***
HAM-A without sleep	***3.57 (3.74)***	***9.25 (3.92)***	***0.013***

Figure RF-4: Mean Improvement in PSQI Total Sleep Score (PSQI SS) *p<0.05, **p<0.075

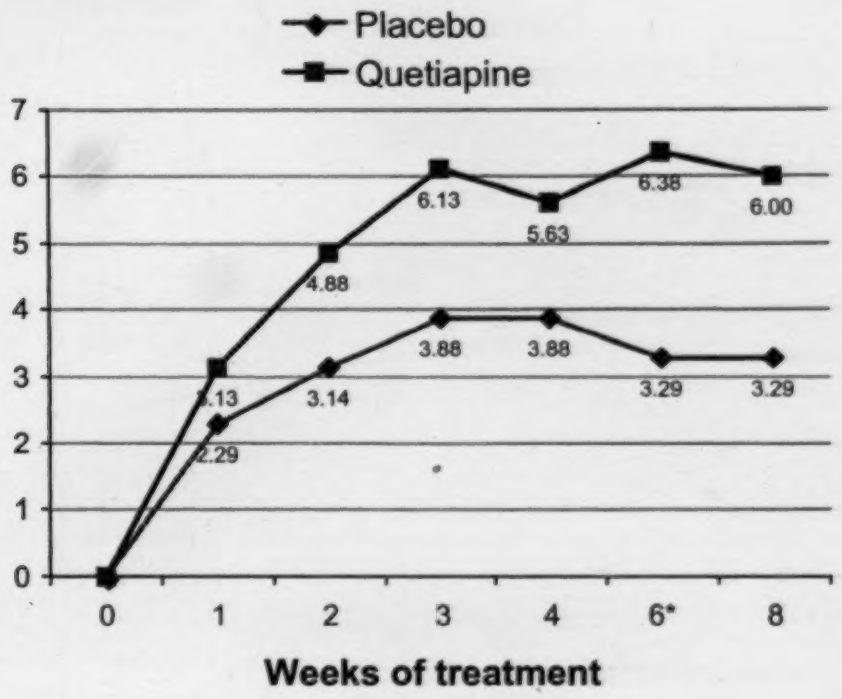


Figure RF-5: Mean Improvement in PSQI-3 (Hours of Sleep)
****p<0.05, **p<0.075, LOCF ITT analysis***

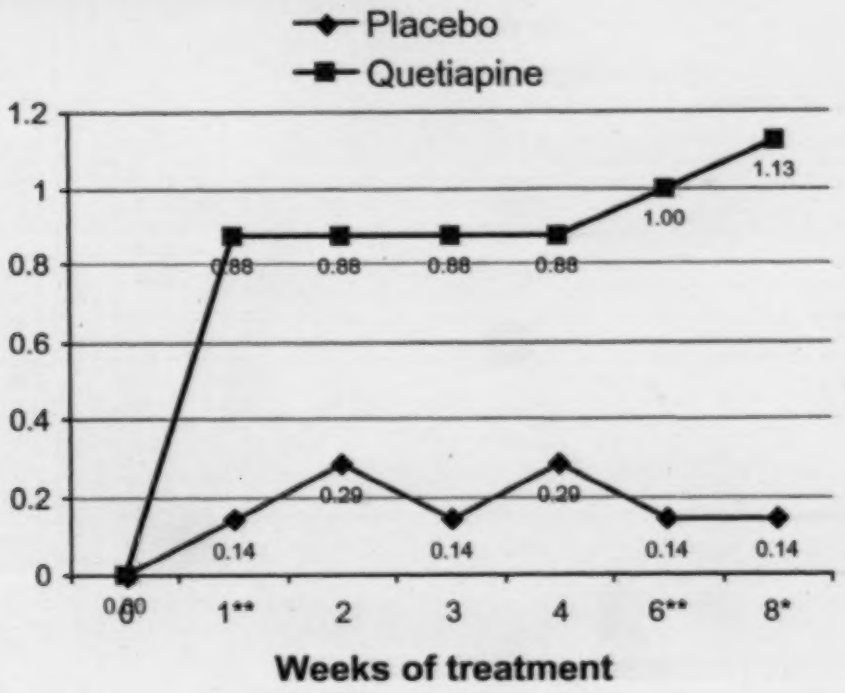


Figure RF-6: Mean Improvement in PSQI-4 (Sleep Efficiency)
****p<0.05, **p<0.075, LOCF ITT analysis***

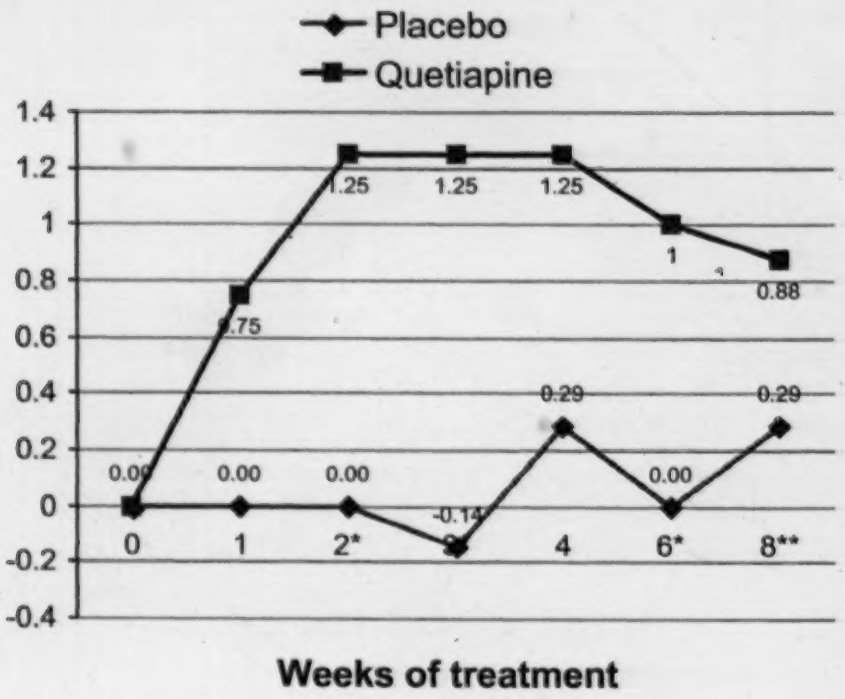
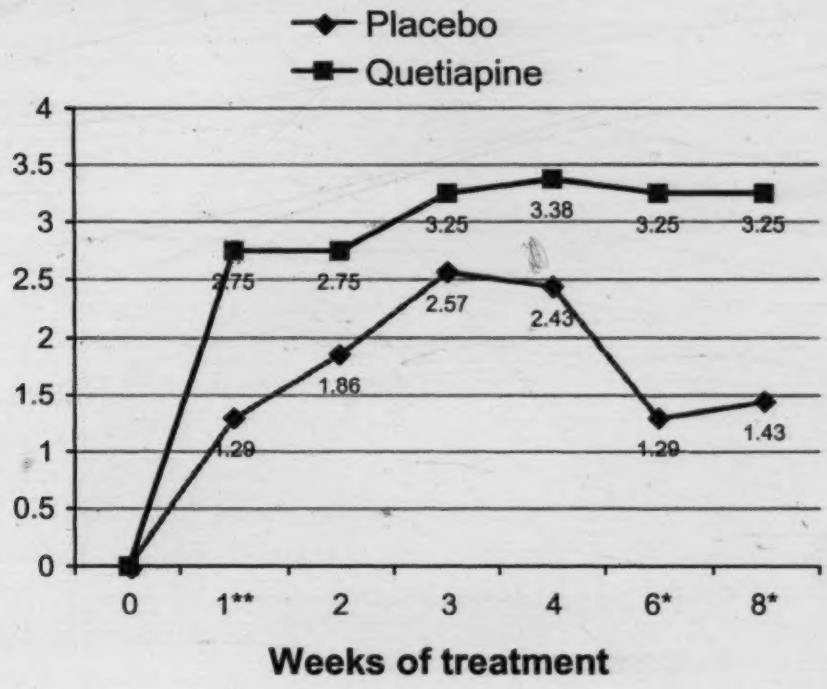


Figure RF-7: Mean Improvement in HAM-D17 Sleep Score (HAM-D17 SS) *p<0.05, **p<0.075



Subanalyses

One must be cautious with interpreting the results of subanalyses of individual items on the scales given the small sample size and that corrections for multiple comparisons were not made. However, some interesting trends can be seen. On the HAM-D17, significant changes were seen for the quetiapine group on the items of guilt feelings, gastrointestinal somatic symptoms and general somatic symptoms (Table RT-8). The sleep subscales have already been noted previously (Table RT-7).

Table RT-8: Mean Change in Individual HAM-D17 Scores Over 8 Weeks (standard deviation in brackets)

	Placebo (n=7)	Quetiapine (n=8)	p value
Depressed mood	0.71 (0.76)	1.13 (0.64)	0.275
Feelings of guilt	*0.00 (0.58)*	*0.75 (0.71)*	*0.044*
Suicide	*-0.14 (0.69)*	*0.38 (0.52)*	*0.121*
Work and activities	0.71 (0.49)	1.00 (1.20)	0.566
Retardation	0.29 (0.49)	0.63 (0.52)	0.216
Agitation	0.71 (0.76)	0.50 (0.53)	0.533
Anxiety psychic	0.43 (0.53)	0.75 (0.89)	0.420
Anxiety somatic	0.14 (0.69)	0.75 (0.89)	0.167
Somatic symptoms GI	***-0.14 (0.38)***	***0.50 (0.53)***	***0.020***
Somatic symptoms general	***-0.29 (0.95)***	***1.00 (0.76)***	***0.012***
Genital symptoms	0.29 (0.49)	0.50 (0.76)	0.533
Hypochondriasis	0.71 (0.95)	0.63 (1.06)	0.867
Loss of weight	-0.29 (0.49)	-0.13 (0.83)	0.663
Insight	0 (0)	0 (0.53)	1

On the MADRS, significant changes were seen for the quetiapine group on the items of reduced appetite, lassitude as well as trends towards the significance for the items of tension and pessimistic thoughts (Table RT-9).

Table RT-9: Mean Change in MADRS Scores Over 8 Weeks (standard deviation in brackets)

	Placebo (n=7)	Quetiapine (n=8)	p value
Apparent sadness	0.57 (1.13)	1.25 (0.89)	0.216
Reported sadness	1.43 (0.79)	1.63 (1.19)	0.716
Inner tension	*0 (1.41)*	*1.25 (1.28)*	*0.096*
Reduced sleep	0.71 (1.60)	2.88 (1.36)	0.014
Reduced appetite	***0 (0.58)***	***1.63 (1.60)***	***0.025***
Concentration difficulties	0.86 (1.58)	1.38 (1.30)	0.498
Lassitude	***0.57 (1.51)***	***1.88 (0.64)***	***0.044***
Inability to feel	0.86 (0.69)	0.75 (0.89)	0.800
Pessimistic thoughts	*0.14 (1.07)*	*1.13 (1.13)*	*0.108*
Suicidal thoughts	0.29 (0.95)	1 (0.93)	0.165

On the HAM-A, significant changes were seen in the quetiapine group for the items of tension, autonomic symptoms as well as a trend toward significant improvement on the behavior at interview item (Table RT-10).

Table RT-10: Mean Change in Other HAM-A Scores Over 8 weeks (standard deviation in brackets)

	Placebo (n=7)	Quetiapine (n=8)	p value
Anxious mood	0.29 (0.49)	0.63 (0.52)	0.216
Tension	*0.14 (0.69)*	*1.13 (0.99)*	*0.047*
Fears	0.43 (0.79)	0.25 (0.71)	0.651
Intellectual (cognitive)	0.57 (1.27)	1.13 (0.35)	0.257
Depressed mood	0.71 (0.95)	1.13 (0.83)	0.389
General somatic (muscular)	0.71 (1.11)	1.25 (0.71)	0.279
General somatic (sensory)	0.86 (1.07)	0.75 (0.89)	0.835
Cardiovascular symptoms	-0.14 (0.38)	0.25 (0.71)	0.212
Respiratory symptoms	-0.29 (0.49)	0 (1.20)	0.566
Gastrointestinal symptoms	0.14 (0.69)	0.50 (0.53)	0.279
Genitourinary symptoms	0.14 (0.69)	0.38 (0.74)	0.544
Autonomic symptoms	*0 (0.82)*	*1 (0.93)*	*0.046*
Behavior at interview	*0.14 (0.69)*	*0.88 (0.64)*	*0.053*

In terms of adverse effects, quetiapine was well tolerated and there was only one dropout that was directly due to an adverse event. The medication was well-tolerated, with somnolence being the largest concern (Table RT-11).

Table RT-11: Major Adverse Events (AE) (number in brackets: AE continued until end of study)

Adverse Event	Placebo	Quetiapine
Drowsiness	4 (2)	7 (4)
Headache	5 (2)	3 (1)
GI (nausea, diarrhea, heartburn)	3 (1)	3 (1)
Weight gain	0	1 (1)
Worsening of mood	2 (1)	1 (0)
Muscle cramps in legs	1 (0)	1 (1)
Dry mouth	1 (1)	1 (1)

Discussion

A sizeable minority (100/326, 30.68%) of patients were found to be unsuitable for the trial during telephone screening simply because their AD dose had not been titrated to a therapeutic level (Table MT-1). This was surprising given the amount of education given to physicians about dose optimization of ADs. This may also speak to a need for further depression education in our area. The relatively large proportion of bipolar II disorder (25% or 6/24) that was elucidated during clinical interviews speaks to the recent lines of evidence indicating that many patients who present with residual depression or TRD often actually have bipolar disorder (135).

Our overall randomization rate of 16/24 (66.7%) is comparable to the 58/73 (79.5%) in another study of this nature (79). Our total completion rate was 13/15 (86.67%), which is excellent compared to the 34/58 (58.62%) — 18/29 (treatment) and 16/29 (placebo) — in that study (79). It is also interesting to note that there was only one dropout in another published double-blind placebo-controlled study of adjunctive quetiapine and AD medication, but this was done with OCD patients (66).

The dose of quetiapine in its various guises as a mood stabilizer, antipsychotic, hypnotic, anxiolytic and antidepressant are a subject for significant debate. The average dose of 350mg in this study was towards the higher side of dosages

used in augmentation trials, but there was a fairly even distribution from 100mg to 600mg. Other double-blind NPUD augmentation trials in depression had lower average doses of 186mg (79), 268mg (80) and 334mg (81). The average in the single-blind trial was 60mg, but this study was fundamentally different in nature (77). First of all, it was done on people without treatment prior to enrollment who were then treated with either the SSRI paroxetine or paroxetine + quetiapine, so a comparison cannot really be made. The other open combination trial similar to this adding quetiapine on to ADs had an average dose of 340mg (78), but a substantial minority of bipolar II patients, hospitalization of all patients and rapid AD titration in this study may have affected this.

Open trials of quetiapine augmentation in NPUD have also demonstrated marked variability in dosage as well. A 20-week open trial had an average dose of 315mg (76). However, these patients appeared to be much more ill than ours, with two failed trials of ADs from different classes and a starting HAM-D of 38.83, which would be considered very severe depression (76). The open trial comparing quetiapine augmentation to lithium (75) had patients with residual symptoms after 4 weeks of AD therapy at a maximal dose and their average dosage was 400mg. However, this was not a flexibly dosed trial.

Case series of adjunctive quetiapine in NPUD had average dosages of 180mg (72) and 275mg (73). However, it is interesting to note that the inclusion criteria in these studies allowed patients who had not been at generally accepted

therapeutic levels of antidepressant treatment. This may have skewed the results towards a lower dose to some degree, although one of these studies was in adolescents, who may have responded to lower doses in any case. The only other published study of quetiapine in adolescent mood disorders utilized a dose of 460mg, but most of these patients had bipolar disorder and the inclusion criteria included a significant number of hypomanic as well a depressive symptoms (136).

In terms of quetiapine dosage in other areas with depressive symptoms, the landmark monotherapy studies with quetapine in bipolar depression used both 300 and 600mg groups. There was not a large difference between the efficacy or effect sizes of the groups (34, 35). The 2 controlled trials of quetiapine augmentation in borderline personality disorder, in which depressive symptoms play a large part, used doses of 251mg (64) and 540mg (65). In the treatment of anxiety disorders quetiapine dosages ranged from 100-125mg in GAD (71), social phobia (69,70) and PTSD (62,63) to 300mg in OCD (66). The study of quetiapine in primary insomnia had a very low dose range of 25-75mg (115), but as mentioned previously, these people were free of major mental illness.

Overall it appears that the dosage levels of adjunctive quetiapine in NPUD likely have a wide range. This is not surprising given that the dosage levels of quetiapine in schizophrenia, its primary indication, are still a matter of debate (137). Dosages are likely dependent on the design of the study, inclusion

criteria, the level of residual symptoms and previous treatment. Comparisons within trials must take these factors into consideration, and further standardization in inclusion criteria and study design in NPUD augmentation trials is needed. Guidance in quetiapine's dosage range in widespread clinical use may come from a recent abstract demonstrating the average dosing of adjunctive quetiapine in a hospital population of primarily mood and anxiety disorders patients was 169mg, but 48% of patients received more than 300mg (138).

Table DT-1: Comparison of Major Outcome Measures in Double-Blind Quetiapine Augmentation Studies

Results	Current Thesis[1]	McIntyre (79)[2]	Mattingly (80)[3]	Anghelescu (81)[4]
Mean HAM-D17 change (treatment)	11.88	11.2	16.7	14.1
Mean HAM-D17 change (placebo)	4.86	5.5	9.8	8.1
Difference between groups	7.02	5.7	6.9	6.0
P value	.016	0.008	<.01	<.05
Mean HAM-A change (treatment)	11	12.5	ND	ND
Mean HAM-A change (placebo)	4.14	5.9	ND	ND
Difference between groups	6.86	6.6	ND	ND
P value	.007	.002	ND	ND
Mean MADRS change (treatment)	14.88	ND	17.1	ND
Mean MADRS change (placebo)	5.2	ND	8.7	ND
Difference between groups	9.68	ND	8.4	ND
P value	<.007	ND	<.02	ND

ND=no data, NS=not significant
[1] n=15 (8 treatment, 7 placebo)
[2] n=58 (29 treatment, 29 placebo)
[3] n=40 (26 treatment, 14 placebo)
[4] n=34 (18 treatment, 16 placebo)

Given the limited sample size, it was surprising that such a strongly significant effect for the quetiapine group was seen on a number of outcome measures in the current study. The magnitude of total and mean improvement between treatment and placebo groups on the primary outcome measure (HAM-D17) correlates very well with the other studies of similar design (79-81) and larger sample size (Table DT-1). However one study (81), only reported a completer, not a LOCF analysis. Another study (79) had an anxiety inclusion criteria of HAM-A > 13 and HAM-D17 > 17, which were more stringent than ours. However, all of our patients except one would have fulfilled these increased criteria. One study showed a similar difference with greater total change in both groups (80). This may be due to the fact that patients in this study appeared to have more severe depressive symptoms on entry (HAM-D17 of 25.0, 24.5 for placebo and treatment groups respectively).

The mean improvement in HAM-A and MADRS in the current study for treatment and placebo groups also compares well to the other studies (Table DT-1). Again there was a larger numerical change in the one study that reported the MADRS (80) and perhaps again this was due to more severe illness in the initial sample. One double-blind study (79) did not use the MADRS as an outcome measure and the other did not use the HAM-A (80) as outcome measures. The current thesis used both. Overall it appears that the significant improvement for the quetiapine group versus placebo in the current study is very comparable to the above studies of similar design.

Our results were also in line with the aforementioned single-blind study of different methodology, where the mean difference between the paroxetine and paroxetine + quetiapine groups was 7.3 on the HAM-D17 and 6.8 on HAM-A. Numerically the total mean decreases in each group were much higher (19.9 and 26.7 for the HAM-A, 14.6 and 21.9 for the HAM-D17; paroxetine and paroxetine/quetiapine treatment groups respectively) (77), but these people were also much more ill (initial mean HAM-A 31.9 and 33.6; HAM-D17 23.9 and 28.0 for paroxetine and paroxetine/quetapine groups respectively). It is likely that quetiapine augmentation may have been ameliorating some initial paroxetine side effects in some patients. The changes in HAM-D17 and HAM-A in the double-blind quetiapine augmentation trial of OCD were also significant, but smaller. However, depression and anxiety were secondary outcome measures in this study and not as severe at baseline (60). The open studies of quetiapine augmentation in NPUD demonstrated vastly greater changes in depression and anxiety outcome measures (75, 76), but this is a common finding of open non-blinded studies compared to controlled trials.

Table DT-2: Comparison of Remission and Response Rates Between Double-Blind Trials of Quetiapine Augmentation to SSRI/SNRI Treatment

Results	Current Study	McIntyre (79)	Mattingly (80)	Anghelescu (81)
HAM-D response in treatment group (%)	50	48	67	60
HAM-D response in placebo group (%)	32	28	27	51
P value	NS	NS	**<.02**	NS
HAM-D remission in treatment group (%)	37.5	31	**43**	**42**
HAM-D remission in placebo group (%)	0	17	15	**26**
P value	.07	NS	**<.05**	**<.02**
HAM-A response in treatment group (%)	50	**62**	ND	ND
HAM-A response in placebo group (%)	14	**28**	ND	ND
P value	.143	**.02**	ND	ND
HAM-A remission in treatment group (%)	**50**	41	ND	ND
HAM-A remission in placebo group (%)	**0**	17	ND	ND
P value	**.03**	NS	ND	ND

ND=no data, NS=not significant

Given our small sample size it was difficult to generate meaningful response and remission rates. Nevertheless, significant trends were seen for the quetiapine group, showing greater response and remission rates on a variety of outcomes even though only HAM-A remission rates were significantly different. These are also comparable with the other studies (Table DT-2). The HAM-D17 response rates of the current study for the quetiapine and placebo group respectively compared well to one study (79) and not as well to the others (80, 81). In terms of HAM-D17 remission rates, the numbers are more comparable. No one in the current study remitted in the placebo group, but this may have been due to the small sample size. In terms of HAM-A response rates, the current study demonstrated a level lower than the other studies, but in terms of HAM-A remission rates it was comparable. Again, no one remitted in our placebo group, and this could have falsely led to statistical significance. Open trials have demonstrated response and remission rates in the 70-90% range (75, 76), but again this is often seen with these trials in the psychopharmacological literature. Overall, our remission and response rates for both treatment and placebo groups are very consistent with a recent metanalysis of AAP augmentation in treatment-resistant NPUD (response 57.2% vs 35.4% respectively; and remission 47.4 vs. 22.3%, respectively) (138a).

Expressing remission in a more clinically meaningful way can be done by a concept called number needed to treat (NNT). In the one comparable study to the current trial, the NNT was calculated to be 7 for remission of depression and

4 for remission of anxiety symptoms (79). This would mean that 7 patients with residual symptoms of NPUD on SSRI/SNRI treatment would have to be augmented with quetiapine to achieve 1 remission on the HAM-D17 versus treatment with placebo. Similarly, 4 patients would have to be augmented with quetiapine in order to achieve a remission of anxiety. Given the similarity of our overall results, even though the sample size of the current study is too small to make a NNT meaningful, a similar level could be approximated. These results are very comparable to the large well-controlled bipolar depression trials where the NNT to reach depressive remission was 5 (139). To put this into perspective, these NNTs are orders of magnitude better than commonly accepted treatments in other branches of medicine. For example, lowering blood pressure with antihypertensives to prevent heart attacks often show a NNT of 40-100 (140).

The other double-blind studies saw positive results for the quetiapine groups as early as week 1 (79, 80) and week 2 (81). However, the current study did not show statistically significant separation until week 4. Again this may have been due to sample size, but perhaps a true AD effect consistent with a longer duration of action rather than a sleep improvement, which would occur right away, was being observed. This separation at week 4 is consistent with the open trial comparing adjunctive quetiapine to lithium augmentation, where statistical separation of quetiapine response and remission rates from lithium happened at a similar point in time (75).

There were no differences between the groups on mean change of weight metabolic parameters. However, it was noted that 6 people in the treatment group gained a significant amount of weight (more than 1.5kg) whereas only 2 subjects in the placebo group did. It is quite likely that a trial length of 8 weeks is not long enough to truly do justice to the deleterious metabolic effects of the AAP. Other studies of similar design with quetiapine have not demonstrated statistically significant weight changes (79, 80), but again the longest placebo-controlled study has only been 8 weeks. Another hypothesis could be that mood disorder patients may have a different level of vulnerability to weight gain than schizophrenics, on whom most of the metabolic evidence base of the AAPs is based. However, a recent study of large health care databases that included all patients on AAPs indicates similar deleterious metabolic changes (141), possibly refuting this hypothesis.

Given the strength of change in other outcomes, it was surprising that the PSQI was not significant. However, the quetiapine group did show significant separation in week 6, certain subanalyses of individual items of the PSQI were positive and there was an overall trend towards significance. Subanalyses of this type can be misleading, especially with a small sample size, but they may point out interesting trends and were identified prospectively as outcome measures. The sleep subscale of the HAM-D was significantly better in the treatment group, but this was powered entirely by an improvement in middle insomnia. This correlates well to the subscales of the PSQI that improved significantly in the

quetiapine group (hours of sleep and a trend towards sleep efficiency). Quetiapine also improved these PSQI subscales in the patients with primary insomnia (115), and also demonstrated beneficial change on PSQI subscales of sleep quality and sleep latency, which the current study did not. The finding of the current study is further supported by an objective increase of total sleep time and sleep efficiency using quetiapine in both healthy patients and patients with primary insomnia (114, 115).

The other double-blind NPUD augmentation study to report its individual HAM-D17 sleep subscale results demonstrated change for the quetiapine group on all 3 sleep items (79), and one open study (76) demonstrated a rapid change in the total HAM-D sleep subscore. There was also a marked improvement with quetiapine on measures of actigraphy (78), but this is a crude measurement of motor activity at night and often does not accurately indicate sleep. That study was also problematic on a number of fronts, primarily because it was not true NPUD augmentation treatment. As mentioned previously, the study washed out all medications in hospitalized subjects over 2 days and then started them on a rapid AD titration plus escalating doses of quetiapine (78). Withdrawal symptoms from washout, symptoms from the rapid titration of antidepressant and the open nature of the trial all could have contributed to a significantly exaggerated effect of quetiapine. Retrospectively the authors concluded that the effect of quetiapine was not due to a sedating effect, because improvement in sleep parameters did not correlate with the mood improvement group. This is a risky post-hoc

assumption. Also, a significant proportion of the group had bipolar II depression (23%) and given recent data (34, 35), quetiapine may be more effective against bipolar disorder rather than unipolar depression. Hence it is quite difficult to understand the true findings of that study on sleep.

The HAM-A and MADRS sleep scores were also significantly better in the quetiapine group, but indication of a sleep-independent mechanism of the agent was seen. Subanalyses of HAM-D, HAM-A and MADRS without the sleep variables all still demonstrated strongly significant changes for the treatment group. Although trends were seen in weeks 1 and 2 for improvement in sleep in the current trial and that change is consistent with other studies (76,79), it took until week 6 to see consistent results on many scales of sleep, and it was ultimately on the mood subscale that PSQI demonstrated the most significant difference. Nevertheless, AAP augmentation of AD therapy has clearly shown improvements for NPUD patients in objective measures of sleep (108, 109). Given the fact that subjective and objective ratings of sleep correlate poorly with treatment response in depressed patients (142, 143), it is quite possible that these agents may have improved mood without a discrete parallel improvement in subjective sleep scales.

It is interesting to note that of the individual HAM-D and HAM-A score subanalyses, 3 of the 6 positive items in the current trial—guilt and somatic anxiety on HAM-D, as well as tension on HAM-A—were seen in an similar study

(79). This is supported further in our trial by the trend towards significance in the similar items of tension and pessimistic thoughts on the MADRS. What was not seen in the previous study compared to the current trial was a significant improvement in the HAM-D17 somatic gastrointestinal (GI) symptoms subscale. This improvement may be due to the well-known appetite stimulating properties of the AAP. This was echoed in our trial by a significant increase on the MADRS appetite subscale for the quetiapine group. Further support comes from the quetiapine NPUD augmentation trial with somatic symptoms, where a high level on the somatic anxiety and somatic GI symptom subscales were inclusion criteria. These subscales also demonstrated significant improvement with the quetiapine group (81), which was consistent with our study. Perhaps the appetite stimulating effects of the AAP lead to improvement on clinical scales of depression, magnifying their true AD effect. Another related concern is that AAP augmentation studies of NPUD demonstrate that the AAPs in question may simply be treating other sub-clinical psychopathology rather than depression such as anxiety disorders (74). It is very difficult in clinical trials to isolate depression from anxiety but given that this is clinically common, likely this lack of separation is only crucial for internal validity. Overall, the current trial indicates that the quetiapine augmentation treatment in NPUD appears to have a wide range of symptom control in areas besides sleep, similar to its effect in bipolar depression.

Mechanisms

Quetiapine and the other atypicals have multiple receptor effects that are theorized to impact their improved efficacy in a number of symptom domains of NPUD. The reader is referred elsewhere for a more extensive discussion (144-146), but pertinent lines of evidence will be discussed here as they relate to the findings in adjunctive treatment of non-psychotic unipolar depression.

Serotonin (5-hydroxytryptamine)

There is consistent evidence that dysregulation of the 5-HT system as a whole is linked to a causative role in depression (147), and the SSRIs are well-established effective agents in the treatment of depression (5). Quetiapine has multiple actions on the serotonin system and has one of the strongest serotonergic actions of the AAP group (148), with an affinity for serotonin receptors that is considerably greater than for dopamine receptors (149, 150). The prevailing theoretical mechanism of the antidepressant effects of quetiapine is 5-HT2A receptor antagonism (144). Quetiapine demonstrates strong 5-HT2A receptor antagonism in patients with schizophrenia (150, 151), an effect common to members of the AAP group (152, 153). 5-HT2A receptor antagonism has been shown to increase extracellular serotonin levels in the prefrontal cortex (154) and to result in successful treatment of symptoms of depression in animal models (155). This mechanism is also common to many clinically proven AD such as mirtazapine, nefazodone and trazodone (156-159). Trazodone itself is used as a common augmenting agent clinically, although formal evidence is lacking. The above 3 ADs are known to have beneficial effects for sleep and anxiety as well

as a lack of sexual dysfunction seen with other serotonergic ADs. (159, 160, 161) It is this 5-HT2A receptor antagonism that has been consistently theorized to be a part of these effects (162-164) and has also been directly linked with improvements in anxiety and AD-induced sexual side effects (165, 166).

With regard to sleep, 5-HT2 receptor antagonism has demonstrated an increase in slow wave sleep and REM latency as well as an overall suppression of REM sleep (167-169). REM suppression and increased REM latency are features that are almost universal among ADs, although the actual relation to their efficacy is unclear (110, 110a). These findings are so robust that they are frequently used as markers in animal studies for potential development of new AD molecules (170). REM suppression and increased REM latency have been seen for risperidone (109) in NPUD patients and ziprasidone (105) in healthy volunteers. An increase in slow wave sleep is also thought to be linked to improved well-being and only seen with a few ADs (110, 110a). As mentioned previously, slow wave sleep increase for olanzapine (108) has been seen in NPUD patients and healthy controls (102, 103). Quetiapine has demonstrated significant REM suppression as well as a trend towards increased REM latency in one study of healthy people (114), but no reputed changes in the other study of people with primary insomnia (115). Further clarification of this mechanism is needed, but since quetiapine has been reported to promote sleep and decrease anxiety in the current trial and others it would be reasonable to speculate that this is partially due to 5-HT2A receptor antagonism.

Another piece of evidence linking the 5-HT2A receptor blockade of quetiapine to its AD qualities is the downregulation of 5-HT2A receptors in response to antagonism. This is thought to be a strong indicator of successful AD treatment (147) and occurs with several ADs from different pharmacological classes; olanzapine and electroconvulsive therapy (ECT) also demonstrate this (144). Given its potential AD effects, it is thus no surprise that the quetiapine has also been seen to downregulate 5-HT2A receptors (171).

Another putative mechanism involving the serotonin system includes 5-HT1A receptor agonism. Animal models show that 5-HT1A receptor agonists are anxiolytic (172), and buspirone and gepirone, strong 5-HT1A receptor agonists, are clinically used in humans for the treatment of anxiety and depression states. (173-175). Quetiapine (176) and its metabolite norquetiapine (177) both have significant 5-HT1A receptor agonism. Ziprasidone, an AAP with very strong 5-HT1A receptor agonist activity (153), has demonstrated anxiolytic efficacy equivalent to 10mg of diazepam in a double-blind placebo-controlled comparison trial (178). That study is also notable in that unlike valium, ziprasidone had no significant sedative effects compared to placebo. Benzodiazapines are well known to mediate many of their anxiolytic and sedative effects through the GABA-A receptor, but ziprasidone has no action at this site (178). This may indicate that the mechanisms of anxiolysis and sedation can be separated and anxiolytic effects without sedation could quite possibly involve the 5-HT1A

receptor. Given that quetiapine has often shown robust anxiolytic effects without corresponding sedation in many of the previously mentioned studies, this leads to the theory that 5-HT1A agonism may be involved in some way.

Noradrenaline (Norepinephrine, NE)

Multiple lines of evidence have been seen linking a deficit of NE to depression. Many successful ADs such as mirtazapine, reboxetine, and to some degree venlafaxine and duloxetine can increase extracelluar NE through reuptake inhibition (179). The successful drug for attention-deficit disorder, atomotoxetine, also increases NE in the brain (180). Quetiapine has demonstrated an increase in extracellular NE in the rat brain and this is thought to be due to alpha 2 noradrenergic autoreceptor antagonism (181). An increase of serotonin has been demonstrated, with risperidone potentially using this mechanism (182). Newer studies indicate that a metabolite of quetiapine, norquetapine, significantly inhibits NE reuptake transporters in vitro (177). The findings above could underlie some of the mood lifting effect and increased attention in patients who use quetiapine in depression. The presence of active metabolite with a strong effect on various neurotransmitters is also commonly seen in various ADs and appears to be unique for quetiapine among the AAPs, furthering the hypothesis that the agent can act like an AD (145).

Dopamine

From the earliest days of psychopharmacology, dysfunction of the dopamine system has also been significantly linked to depression. Older ADs such as the monoamine oxidase inhibitors (MAOIs) are well known to increase dopamine levels in the brain (158) and the well-established AD fluoxetine has been reported to increase extracellular dopamine in the rat prefrontal cortex (PFC). (183). Venlafaxine, bupropion and sertraline also have effects on dopamine reuptake that results in an increase of available dopamine (158). The 5-HT1A receptor agonism and, to a lesser extent, 5-HT2A receptor antagonism of quetiapine have also been seen to increase dopamine in the rat PFC (176, 184), although this finding has not always been notable (185). The PFC is a neuroanatomic area that has been strongly linked with mood (186) and an increase of extracellular dopamine there has been demonstrated to increase mood. A decrease in negative symptoms in psychotic states has also been noted with an increase of DA in the PFC (187), which overlaps to some degree with neurovegetative signs of depression.

Rapid dissociation from the D2 receptor, or the "on-off" phenomenon, is evident with quetiapine (148), and has been postulated as a reason for the agent showing less antipsychotic-induced dysphoria than many other APs and AAPs (146). Tests of the AAPs on a recent animal model of drug-induced dysphoria supported this, as quetiapine and clozapine, which also has minimal D2 receptor blockade, were the only two AAPs to not cause the effect (188). Further evidence comes from the finding that risperidone and the typical APs, both with

mixed results in the treatment of depression, show much stronger D2 antagonism and binding than olanzapine (152), which has shown consistent benefit in the treatment of depressive syndromes. The stronger dopamine blocking potential of risperidone could cause a dysphoria, which stymies the AD effect of its 5-HT2A receptor antagonism and increase of PFC dopamine. Perhaps similar mechanisms combining 5-HT2A receptor antagonism, the increase of dopamine in the PFC, and the lack of antipsychotic-induced dysphoria could be contributing to the more consistent antidepressant effect of quetiapine seen in clinical trials.

Histamine

Quetapine has strong H1 histamine receptor blockade. It is unclear what this does for mood, but it may promote sleep and increase appetite similar to other histamine H1 antagonists. A theory has recently been put forth that this antihistaminergic mechanism of quetiapine may mediate AD effects (144) by a decrease in inflammatory cytokines, improving many depressive symptoms that cytokines are reported to cause (189).

Glutamate

Downregulation of the N-methyl-D-asparate (NMDA) receptors of glutamate are a consistent feature of several ADs (190) and NMDA receptor antagonists are noted to cause significant AD-like effects (191). Quetiapine, olanzapine and risperidone have all been shown to downregulate NMDA receptors (192) and quetiapine itself has been seen to reduce NMDA receptor subunit expression in

rats (193). These findings have led to the hypothesis that quetiapine and other AAPs may mediate some longer-term AD effect through possibly restoring neural transmission and reducing glutamate-induced excitotoxicity through their effects on these receptors (144).

Neuroprotective mechanisms

Brain-derived neurotrophic factor (BDNF) plays an important role in neuronal cell repair and strength. Chronic AD treatment has been seen to start a cascade of events that increases the expression of BDNF (194). Stress paradigms have been reported to decrease this in the hippocampus of rats (195) and decreased levels of serum BDNF have been seen in depressed patients compared to controls (196). Quetiapine has been shown to be significantly associated with increased BDNF expression in the rat hippocampus (197), and is also linked with the prevention of a stress-induced decrease of BDNF expression in this region (198, 199). The agent has also been linked to an increase in BDNF and other growth factors in the rat hippocampus in response to an NMDA antagonist (200), which, as mentioned previously, can produce a depressed state.

Recent trials in rats have shown other possible neuroprotective properties of quetiapine. These include attenuation of memory impairment and hippocampal neurodegeneration induced by brain hypoxia (201), a decrease in depressive and anxiety symptoms induced by global cerebral ischemia (202), as well as a facilitation of neuronal growth (203). There are also data demonstrating

prevention of apoptosis in animal models as well (204, 205). This is especially interesting given a recent open trial showing efficacy of quetiapine augmentation for depression in elderly patients with cerebrovascular damage (206). Hence the AD effects of quetiapine may have something to do with BDNF transcription, neuroprotection and neurogenesis. Given the biochemical nature of these systems, this is probably linked more to a delayed AD effect.

HPA axis

It is well known that subjects with mood disorders have a high incidence of Hypothalamic-Pituitary-Adrenal (HPA) axis abnormalities such as an elevated cortisol and demexathesone non-suppression (207, 208). Antidepressants are seen to normalize this to some extent (209). Quetiapine has also shown to normalize some of these indicators of HPA dysfunction in healthy people (210, 211). It can lower cortisol as well as decrease plasma levels of adrenocorticotrophic hormone (ACTH), which is another significant marker of HPA overactivity. Olanzapine also demonstrated this as well, but the typical AP haloperidol did not (211). This effect was postulated to be due to the blockade of 5-HT2, alpha 1 adrenergic and/or histaminic receptors. Normalization of the HPA axis may also help cognition as overactivity can raise the levels of glucocortocoids, which can lead to cognitive dysfunction and depression (208, 212). Looking further at steroid-type molecules, an increase in the level of the neurosteroid allopregnanolone has also been postulated as a sleep and mood improvement mechanism for quetiapine (114), as it has improved learning,

memory and depressive symptoms in animal models (213). However, a recent study indicated that only olanzapine and clozapine, but not quetiapine, increased levels of the related steroid pregnanolone in the rat brain (214), casting doubt on this theory.

Synergism

Often when an AAP is added to an AD, synergistic effects on brain function can occur, potentially explaining the improvement in mood. For example, when added to fluoxetine, risperidone causes a synergistic rise in dopamine, and olanzapine causes a rise in both extracellular dopamine and noradrenaline in the rat PFC (187, 215). A similar effect was seen when risperidone was added to citalopram (216). Quetapine and fluvoxamine also demonstrated this increase in dopamine in the rat PFC synergistically where neither did alone. This was noted to be more transient than the olanzapine and fluoxetine combination and there was no increase in serotonin (185). Hippocampal cell proliferation and prevention of BDNF decrease in a chronic stress paradigm in the rat also increased synergistically with the combination of venlafaxine and quetiapine (217). Higher doses of each agent yielded the same effects, but a lower dose in combination provided the same result. There are also lines of evidence of a synergistic increase in extracellular serotonin when combining SSRI and 5-HT2A antagonists (218, 219). Obviously much of this data is preclinical and speculative, but it does give credence to the possibility that an AAP plus an AD may have truly positive synergistic effects on mood.

Limitations

Major limitations of this study include a very small sample size, but, as discussed previously, there are significant statistical results that correlate well with similar trials of a large sample size. Further trials should consider the possibility of a 2:1 randomization ratio to maximize statistical power in a small number of subjects, as was done in one of the double-blind NPUD studies (80). Adjustments for multiple comparisons were not made, but our sample size was too small to consider this. Also, outcome variables were clearly stated prior to analysis. Usually these adjustments are needed for ad-hoc secondary analysis of data that was not stated prior to the study.

The length of the trial was short, but this was due to funding concerns. It is comparable with the length of most other controlled trials of atypical augmentation in NPUD (138a). There was no comparison group with an established sleep agent. Given that much of the AAPs' AD effect may be due to improved sleep, this would be have been valuable. A comparator group with quetiapine monotherapy would have also been useful and potentially provided possible evidence of a synergistic effect. This technique has been used in previous AAP augmentation studies (31). A comparator group of a different AAP or even typical AP could have been used assessing for differential response and effects. Reviewing the data, it may be best to compare quetiapine and olanzapine in future studies.

Another weakness of the current study was the lack of objective sleep monitoring. This could be crucial given that it is well known that subjective reports of sleep correlate very poorly with objective sleep data and treatment response in depressed patients (142, 143). The inclusion of objective sleep monitoring should be a future feature of augmentation trials of this type. Further subjective indicators of sleep quality such as the dysfunctional attitudes and behaviors about sleep (DBAS) (220) or the Athens Insomnia scale (221) may also have been useful.

There was no prospective determinant of residual depressive symptoms. This extends the length of the trial and is difficult to do, but improves internal validity because patients are seen objectively to have residual symptoms within the confines of a clinical trial prior to augmentation. This has been done in previous trials (31, 50) and the recent landmark STAR*D trials are employing this method to establish the success of various augmentation and combination strategies in the clinical treatment of depression. (9, 12-16). Further trials should take this into consideration.

The patients in our study were also not all on one class of AD, but this was thought to enhance external validity at the expense of internal validity. Patients on buproprion, a common antidepressant, were not included because of its sleep disturbance, which quetiapine augmentation would potentially remedy, creating a possible overestimation of quetiapine's benefit A significant limitation was the

lack of self-report scale of mood and anxiety concerns such as the Beck Depression (222) or Zung Anxiety (223) to compare with the clinician-rated scales of mood or anxiety. This would have improved consistency. There has also been some concern in blinded placebo trials with sedative agents that there may be a predictive bias because the placebo is not sedating. This was not seen consistently in the above trial. Another weakness is a lack of clarity about whether this current study was measuring quetiapine augmentation in depression with residual symptoms or treatment-resistant depression. This is likely a reflection of the significant amount of debate and confusion in the literature of what constitutes depression with residual symptoms versus treatment-resistant depression (123, 124). They are likely similar concepts on a continuum, but there are multiple definitions and a lack of clarification as to what either consists of. These terms need to be made more consistent and operationalized, similar to remission and response rates and this is beginning to emerge with various ranking systems (224). This study did not use the term treatment-resistant depression (TRD), but depression with residual symptoms. By the study entry criteria, this level of treatment resistance would be defined as mild, and one could argue that led to the significant results with such a small sample size, but the actual demographics of the study group appeared to have a moderate level of treatment resistance comparable to other similar studies (79, 80).

Strengths of the study include the double-blind placebo-controlled trial methodology and the variety of outcome scales used. Compared to the other

similar studies of quetiapine augmentation in NPUD, our study was the only one to use HAM-D17, HAM-A and MADRS. The focus on parameters of sleep is also a unique aspect of this study as well.

Conclusions

The study is one of the first to show improvement for quetiapine augmentation versus placebo in various measures of mood, anxiety and sleep in NPUD patients. Significant changes were seen within 4 weeks for mood and anxiety and trends towards significant changes were seen as quickly as 1 week for sleep. The results are very consistent with three similar controlled trials of this nature and an immediate future research direction should be to combine these studies into a meta-analysis to improve statistical power and confirm trends that were seen. There were also trends towards significant improvement in response and remission rates on clinical mood and anxiety scales that were again comparable to other similar studies and an overall recent metanalysis of NPUD augmentation in TRD.

Areas of sleep seeing positive change were sleep efficiency, middle insomnia, and hours of sleep. Initial insomnia did not appear to improve. No consistent change in metabolic factors or weight was seen. The treatment was well tolerated overall.

Overall, this study provides further evidence that atypical antipsychotic augmentation in NPUD may be useful and improved dimensions of sleep may play a role. Larger scale trials controlling for the previously discussed factors to confirm this are warranted.

Large-scale monotherapy studies are also underway with quetiapine in NPUD. Given the metabolic concerns with the AAPs, evidence of monotherapeutic effect in NPUD will likely not translate into general or widespread clinical use or replacement of standard AD therapy. However, as an augmentation strategy, the somewhat more beneficial profile and sleep friendly effects of quetiapine may position the agent as the favored AAP augmentation agent for NPUD, or even generally in mood and anxiety. This would especially be the case in Canada, where the metabolically neutral aripipazole and ziprasidone are not available. Indeed, the current market share in Canada for quetiapine (the #1 AAP prescribed for the last two years) may be a reflection of this.

Some potential study parameters to minimize weaknesses are alluded to in the above section, but an ideal study design could begin with three large groups of untreated or TRD patients washed out of medication. They would be treated with one or two trials of ADs at therapeutic doses to prospectively establish TRD or depression with residual symptoms. They would then be randomized to further adjunctive augmentation with placebo, a proven sleep agent without much mood effect (clonazepam or zopiclone), another AP (either a comparator AAP or typical low-potency typical AP) and quetiapine. Objective and subjective sleep measurements should be part of the outcome measures. Adequately powered, this could delineate whether quetiapine has a true mood effect, which is suspected from the various results and mechanistic discussions presented

herein, versus sleep effects. Obviously this would be multidisciplinary and expensive, but much of this type of design is already been used in the ambitious and clinically groundbreaking STAR*D trials (12-16). Given the public health burden of depression, full scientific evaluation of all possible augmentation and combination treatments is a small price to pay to potentially alleviate the suffering of millions of people from NPUD worldwide.

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